IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of: Berzofsky et al.
Application No. 10/532,374
Filed: April 21, 2005
Confirmation No. 4276
For: METHODS TO PREVENT TUMOR RECURRENCE BY BLOCKADE OF TGF-BETA
Examiner: Sheela J. Huff
Art Unit: 1643
Attorney Reference No. 4239-67016-02

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UNITED STATES PATENT AND TRADEMARK OFFICE

DECLARATION OF DR. JAY A. BERZOFSKY UNDER 37 C.F.R. § 1.132

I, Jay A. Berzofsky, M.D., Ph.D declare as follows:

1. I am named as co-inventor of U.S. Patent Application No. 10/532,374, filed April 21, 2005. I have read the above-referenced patent application and the Office action dated February 11, 2009.

2. A copy of my *curriculum vitae* is attached hereto as **Exhibit A**. At present, I hold a position as Chief of the Vaccine Branch, Center for Cancer Research, at the National Cancer Institute. I have 34 years of experience in research including work on immunology and biochemistry, vaccines and cancer. I have published over 435 scientific articles in scientific journals and books. I was president of the American Society for Clinical Investigation from 1993-1994, and was Chair of the Medical Sciences Section of the American Association for the Advancement of Science from 2007-2008. By virtue of my education, training, and professional experience, I am knowledgeable about tumor biology.

3. I understand that the Examiner has rejected the claims of the application for allegedly being obvious over Dasch *et al.* (U.S. Patent No. 6,090,383) in view of PCT Patent Application

No. WO 00/01410, Barbera-Guillem (U.S. Patent No. 6,224,866), Rosenblum (U.S. Patent Application No. 2005/0214307), and Zavada *et al.* (U.S. Patent No. 6,297,041) because the combination of references allegedly teach that a compound can "treat tumor recurrence" (Office action at page 4). However, the claimed invention is not directed to *treating* recurrence of a tumor. Instead, the claimed invention is directed to *inhibiting* recurrence of a tumor. The actions of "inhibiting" and "treating" are very different, as methods of inhibiting a tumor recurrence are prophylactic and are used to prevent a tumor from *developing*, whereas methods of treating a tumor recurrence are directed against an *existing* tumor. Moreover, the effectiveness of an agent for *treating* a tumor recurrence does not predict the effectiveness of the same agent for *inhibiting* the recurrence (see paragraphs 5 and 6, below). Thus, it would not be obvious that the same agent would be effective at both inhibiting and treating a tumor recurrence.

4. The Office action alleges that the specification "equates treatment to inhibition/prevention" because "applicant defines treatment as including prophylactic inhibition" (Office action at pages 4 and 5). I disagree with this assessment. The generic word "treatment" is an all-purpose term that refers to many things, including the use of both agents and therapies to inhibit or treat a disease in a subject and, as discussed above, inhibiting and treating are two completely different actions. The specification states that treatment "[r]efers to both prophylactic inhibition of disease (such as tumor recurrence) and therapeutic interventions to alter the natural course of an untreated disease process, such as a tumor growth. Treatment of a tumor includes, for instance, the surgical removal of the tumor. Treatment of a tumor can also include chemotherapy, immunotherapy, or radiation therapy. Two or more methods of treating a tumor can be provided to a subject in combination. Treatment of a subject includes inhibiting or measurably reducing the recurrence of a tumor" (specification at page 17, lines 11-14). As treatment encompasses both inhibition and intervention, treatment cannot be equated exclusively with inhibition.

5. Inhibiting (or preventing) the recurrence of a tumor is very different from treating a tumor after it recurs. Thus, a distinction must be made between *treatment* and *inhibition* of a tumor recurrence. Agents that effectively cause regression of (treat) a recurrent tumor will not necessarily be effective at inhibiting (preventing) the recurrence itself. For example, agents used

to treat pediatric sarcomas, such as Ewing's sarcoma or Alveolar Rhabdomyosarcoma, are ineffective at inhibiting the recurrence of the tumors in most patients, even if the chemotherapeutic agents are effective at treating the recurrence itself (see Pizzo and Poplack (eds.), *Management of Common Cancers of Childhood*, page 1006, right column, 2002, 4th Ed, Lippincott Williams & Wilkins, Philadelphia, PA; Rodriguez-Galindo *et al*, *Cancer*, 94: 561-569, 2002). Thus, not all agents used to treat a recurrence will be effective at inhibiting a recurrence.

6. The following discussion is a representative example of an agent used to treat recurrence that cannot be used to prevent recurrence. Chemotherapy, usually a platinum-based doublet regimen (cisplatin or carboplatin administered with a paclitaxel, docetaxel, or gencitabine) is the standard of care for locally advanced stage and metastatic non-small cell lung cancer (NSCLC; Schiller *et al., N Engl J Med.*, 346:92-98, 2002). In patients with inoperable *recurrent* local-regionally advanced (stage III) NSCLC, platinum doublet chemotherapy combined with radiation can result in 5-year disease-free survivals of 15-20% (Dillman *et al., J Natl Cancer Inst.*, 88:1210-1215, 1996; Belani *et al., J Clin Oncol.*, 23:3760-3767, 2005). However, the same platinum-based doublet therapy was found in large clinical trials *not to be effective in preventing recurrences* when used in early stage IB NSCLC as "adjuvant therapy" after surgery (Wakelee *et al., Clin Lung Cancer*, 8:18-21, 2006). Thus, one of skill in the art would conclude from this example that therapies that are beneficial in *treating* recurrent tumors are *not necessarily effective in inhibiting recurrence* after treating the disease with primary therapy like surgery.

7. WO 00/01410 discloses the use of an anti-TGF-beta antibody to "to detect or quantify the TGF-β" and that the "[r]esults from these tests can be used to diagnose or predict the occurrence of recurrence of a cancer" (WO 00/01410, page 24, lines 7-9). The Office alleges that simply because WO 00/01410 discloses that antibodies to TGF-beta can "be used in the diagnosis and treatment of proliferating cells and that the diagnosis also includes diagnosing tumor recurrence . . . one of ordinary skill in the art would immediately envisage that the same antibody that can detect tumor recurrence can also be used in treatment of tumor recurrence" (Office action at page 5). I disagree and would not equate "detection" with "inhibition."

Antibodies are unpredictable and one of skill in the art would not be able to predict that an antibody used for detection also would be effective at inhibition (or treatment) of tumor recurrence, without first having demonstrated that the antibody can function to both detect and inhibit (or even treat) tumor recurrence. For example, antibodies to Prostate Specific Antigen (PSA) can be used to measure PSA levels to monitor tumor progression or detect or predict tumor recurrence, but these anti-PSA antibodies cannot be used to treat, prevent, or inhibit tumor recurrence. Accordingly, it would not be obvious from a reference that refers to using an antibody for detection purposes, that the same antibody also would be effective at inhibiting tumor recurrence.

8. In summary, based on my education, training, and professional experience, I believe that the term "treatment" cannot be equated exclusively with the term "inhibition," nor can "detection" be equated with "inhibition." In addition, I believe that it would not be obvious to one of skill in the art that the same agent can be effective at both treating a tumor recurrence and inhibiting (preventing) a recurrence.

9. All statements made herein and of my own knowledge are true and all statements made on information are believed to be true; and further, these statements were made with the knowledge that willful false statements and like are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that any such willful false statements made may jeopardize the validity of the application or any patent issuing thereon.

Date June 5, 2009

Jay A. Berzofsky, M.D., Ph.D.

EXHIBIT A

CURRICULUM VITAE

Name: Jay Arthur Berzofsky

Date and Place of Birth: April 13, 1946, Baltimore, Maryland

Marital Status: Married to Sharon M. Miller; two children
Alexander, April 30, 1974, and Marcus, May 27, 1976

Education:

1967 - A.B., Harvard University (Summa Cum Laude in Chemistry)
1971 - Ph.D., Albert Einstein College of Medicine, Molecular Biology
1973 - M.D., Albert Einstein College of Medicine, Medical Scientist Training Program

Brief Chronology of Employment:

1973 - 1974	Medical Internship (Straight Medicine), Massachusetts General Hospital, Boston, Massachusetts
1974 - 1976	Research Associateship, Laboratory of Chemical Biology National Institute of Arthritis, Metabolism, and Digestive Diseases, National Institutes of Health
1976 - 1979	Investigator ("Expert"), Metabolism Branch, National Cancer Institute, National Institutes of Health
1979 - 1987	Senior Investigator, Metabolism Branch, National Cancer Institute, National Institutes of Health
1987 - 2003	Chief, Molecular Immunogenetics and Vaccine Research Section, Metabolism Branch, National Cancer Institute, National Institutes of Health
2004 – Date	Chief, Vaccine Branch, Center for Cancer Research, National Cancer Institute, National Institutes of Health

Honors/Awards:

Detur Prize, Harvard University, 1964
Harvard College Scholarship, Harvard University, 1964
Phi Beta Kappa, Junior Year, Harvard University, 1966
Summa Cum Laude in Chemistry, Harvard University, 1967
Sophia Freund Prize for Graduate with Highest Cumulative Grade Point Average, Harvard College, 1967
NIH Special Achievement Award, 1982

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Hollister - Stier's Distinguished Lectureship, Washington State University, 1986
J. W. McLaughlin Fund Distinguished Contributions to Immunology Lectureship, University of Texas Medical School, Galveston, 1987
U. S. Public Health Service Superior Service Award, 1988
31st Michael Heidelberger Award and Lecture, Columbia University, 1992
McLaughlin Visiting Professorship, University of Texas Medical School, Galveston, 1992
American Society for Clinical Investigation, President 1993-94
Fellow of the American Association for the Advancement of Science, 1995
Cytokine Interest Group Best Paper of 2000 Award to fellow in lab, 2001
The 2004 Tadeusz J. Wiktor Memorial Lecture, Wistar Institute, University of Pennsylvania, Philadelphia, PA., November 17, 2004
Chair, Medical Sciences Section, American Association for the Advancement of Science, 2007-2008
The Herschel Zackheim Lectureship Award, International Society for Cutaneous Lymphomas, 2007
Distinguished Alumnus of the Year Award 2007, Albert Einstein College of Medicine
NIH Director's Award, 2008
NIH/NCI Merit Award, 2008

Professional Society Memberships:

Association of Harvard Chemists, 1967 - present
New York Academy of Sciences, 1971 - present
American Association of Immunologists, 1977 - present
Undersea Medical Society, 1978 - 1988
American Federation for Clinical Research, 1979 - present
American Society of Biological Chemists, 1980 - present
American Society for Clinical Investigation, 1983 - present,
Secretary-Treasurer, 1989 - 1992
President-elect, 1992-1993
President, 1993-94
Association of American Physicians, 1990 – present
American Association for the Advancement of Science, Fellow 1995-present;
Chair of Medical Sciences Section, 2007-2008
American Association for Cancer Research, 2006 - present
Faculty of 1000, 2006-present

Editorial Positions:

Associate Editor, *Journal of Immunology*, 1980 - 1984
Editorial Advisory Board, *Journal of Molecular and Cellular Immunology*, 1983-88
Advisory Editor, *Molecular Immunology*, 1985 - 1988
Editorial Board, *Peptide Research*, 1987 - present
Transmitting Editor, *International Immunology*, 1988 - 2000
Editorial Board, *Journal of Human Virology*, 1997-present
Consulting Editor, *Journal of Clinical Investigation*, 1998-2005

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Section Editor, *Clinical Immunology*, 2002-2007
Associate Editor, *Clinical Cancer Research*, 2002-present

Professional Committees and Activities:

American Association of Immunologists, Membership Committee, 1981 - 1988
American Association of Immunologists, Chairman of Membership Committee, 1983 - 1988
NIH Clinical Center Compensable Events Committee, 1982 - present
American Society for Clinical Investigation, Council, 1989-1994 (President, 1993-94)
NCI Division of Clinical Sciences Promotion and Tenure Committee, 1995-2001.
NCI Division of Clinical Sciences Research Advisory Group, 1995-2001
NCI Director's Intramural Advisory Board, 1997-99
NIH AIDS Vaccine Research Center Steering Committee, 1997-present
NIH Search Committee for Director of Office of AIDS Research, 1997-98
NIAID Malaria Vaccine Task Force, 1998-present
NCI Vaccine Working Group, Chairman/Organizer, 1998-present
NCI/CCR Immunology Faculty Steering Committee, 2001-present
NCI/CCR HIV & Virology Faculty Steering Committee, 2001-present
NCI/CCR Frontiers in Science Newsletter Editorial Board, 2001-present.
NCI/NIH Committee for Biodefense, founding member, 2001-present.
NCI Center of Excellence in Immunology, Steering Committee, 2003-present.
NIH CRADA 01361 with Genzyme Corporation. Co-principal Investigator, 2003-present
Advisory Committee, Harvard Blood Center, 2004-present
External Advisory Committee, University of London, 2006-present.
NCI Center of Excellence in HIV & Cancer Viruses, Executive Committee, 2006-present
NIAID AIDS Vaccine Research Subcommittee, 2007-present
NIH Director's Biennial Report to Congress, 2007, Team Leader for Cancer topic.
NCI Cancer & Inflammation Program Tenure Track Search Committee, Chair, 2007-2008.
NIAID Laboratory of Malaria Immunology & Vaccines Lab Chief Search Committee, 2008.

Military Service:

Commissioned Corps, United States Public Health Service, 1974 - 1976

Other Research Experience:

Summers,1962 - 1965 Research Assistant, Pediatric Research Unit (H. M. Nitowsky), Sinai Hospital, Baltimore, Maryland
Summer, 1966 Research Assistant, Organic Synthesis Laboratory C. H. Robinson), Department of Pharmacology, Johns Hopkins School of Medicine, Baltimore, Maryland
Summer, 1967 Visiting Scientist, Laboratoire d'Enzymologie (G. N. Cohen), Centre National de la Recherche Scientifique, Gif-sur-Yvette, France

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Medical Licensure: Maryland and Massachusetts

Major Outside Activities (Not permitted by NIH after 2005)

Medimmune, Inc.—Scientific Founder and Chair, Scientific Advisory Board, 1989-2002
Magainin Pharmaceuticals, Inc.—Member, Scientific Advisory Board, 1991-97
Diacrin, Inc.—Member, Scientific Advisory Board, 1993-2002
Pharmadyne, Inc.—Scientific Co-Founder and Chair, Scientific Advisory Board, 1997-2004
Boston University Community Technology Fund—Consultant, 1997-1999
Health Care Ventures, Inc.—consultant, 1998
EMD Pharmaceuticals, Inc.—consultant, 2000-2003
Epivax, Inc.—Member, Scientific Advisory Board, 2000-2004
Therapeutic Devices, Inc.—consultant, 2002-2004
Transform Pharmaceuticals, Inc.—consultant 2002-2005
Celera Genomics, Inc.—consultant 2002-2004
Genencor International, Inc.—consultant 2003-2004.

Major areas of research:

1. Molecular basis of antigen recognition by T lymphocytes
2. Processing of antigens and their presentation by major histocompatibility molecules
3. Structure of antigenic sites on protein antigens
4. Genetic regulation of the immune response
5. Design and development of artificial vaccines based on immunological principles and peptide synthesis or recombinant DNA technology
6. AIDS vaccines and diagnostic techniques
7. Malaria vaccines
8. Cancer vaccines
9. Antigen-antibody interactions
10. Structure-function relationships in proteins and protein conformation.
11. Regulation of tumor immunosurveillance and T cell function by cytokines and regulatory cells
12. NKT cells in the regulation of tumor immunity
13. Mucosal immunity and vaccines
14. Cytokines, chemokines, and TLR ligands as immune modulators and vaccine adjuvants.